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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,316	10/23/2003	Mu-En Lee	HUV-046.02	8228
58475	7590	07/21/2008	EXAMINER	
FOLEY HOAG, LLP PATENT GROUP (w/HUV HMV) 155 SEAPORT BLVD. BOSTON, MA 02210-2600			MACFARLANE, STACEY NEE	
			ART UNIT	PAPER NUMBER
			1649	
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			07/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/693,316

Applicant(s)

LEE ET AL.

Examiner

STACEY MACFARLANE

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 April 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 7-9, 12-20 and 22-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 10, 11, 21 and 31-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Response to Amendment

1. Claims 1, 2, 5, 10, 11, and 21 have been amended, claims 31-34 newly added, as requested in the amendment filed on April 10, 2008. Following the amendment, claims 1-34 are pending in the instant application.

Claims 7-9, 12-20 and 22-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed on August 24, 2007.

Claims 1-6, 10, 11, 21 and 31-34 are under examination in the instant office action.

2. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3. Applicant's arguments filed on April 10, 2008 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections – Including New Grounds Necessitated by Amendment

35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-6, 10, 11, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. As currently amended, Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the active steps and conditions "sufficient for the neural crest cells to differentiate uniformly into smooth muscle cells".

7. Claim 2 is vague and indefinite in its recitation of "immortalized cells". Claim 2 depends from Claim 1 which recites "neural crest cells". It is unclear if the limitation that these cells be "immortalized" requires additional omitted active steps in order to perform the method. On page 8 of Remarks filed April 10, 2008, Applicant states that the amendment to claim 1 obviates the rejection. This is not found persuasive. It is still unclear how the immortalized cells of Claim 2 are related to or derived from the neural crest cells of claim 1.

8. Claims 1 and 10 stand as incomplete for omitting essential elements. On page 8 of Remarks filed April 10, 2008, Applicants argue that the amendments to claims 1 and 10 obviate the rejection. This is not found persuasive. Claims now recite the limitation "under conditions sufficient for the neural crest cells to differentiate uniformly into smooth muscle cells". The claims omit essential elements that are required for one of ordinary skill in the art to be reasonably apprised as to the conditions that are sufficient to practice the method. Thus, the metes and bounds of the claim are not clear.

9. Claim 5 depends from claims 3 and 1 and, as currently amended, recites culturing cells in "complete medium prior to culturing in differentiation medium". There is no antecedent basis for "complete medium" in the parent claims. Claim 3 recites "differentiation medium" and Claim 5 distinguishes this from complete medium. One of ordinary skill would not be reasonably apprised as to the metes and bounds of the method.

10. Claim 21 stands rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the active steps required to support the recitations of formulating. Applicant traverses the rejection on the grounds that the amendment to the parent claim (Claim 10) obviate the rejection. This is not found persuasive as the instant claim recites a "further step of formulating a pharmaceutical preparation". The active steps required for the step of "formulating" are omitted.

11. The term "nearly" in claim 31 is a relative term which renders the claim indefinite. The term "nearly" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

12. Claim 34 is vague and indefinite in so far as it employs the term "Monc-1" as a limitation. This term is appears to be novel within the art and without a reference to a precise deposit number or ATCC cell line number one cannot determine the metes and bounds of "Monc-1". Moreover, because the instant specification does not identify that

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property or combination of properties which is unique to and, therefore, definitive of a "Monc-1" cell, an artisan cannot determine if a compound which meets all of the other limitations of a claim would then be included or excluded from the claimed subject matter by the presence of this limitation.

13. Claims 3, 4, 6, 11 and 32-33 are indefinite for depending from indefinite claims.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

15. Newly added claim 33 recites "the method of claim 1, wherein the conditions comprise culturing in medium that does not include exogenously added active TGF- β 1". MPEP section 2173.05(i) states: Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), aff'd mem., 738 F.2d 453 (Fed. Cir. 1984).

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16. The culturing conditions sufficient for the neural crest cells to differentiate uniformly into smooth muscle cells are not clearly recited by the parent claim (Claim 1). The specification recites the components of the culturing medium as those listed in Table 1 (specification page 14) as well as fetal bovine serum, penicillin, streptomycin and HEPES. The instant specification does not positively recite the specific element of "active TGF- β 1" and therefore claim 33 cannot exclude this component by negative proviso. Since the claim does not have basis in the original disclosure it is rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. As currently amended Claims 1-6, 10, 11, 21 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al. US Patent 5,672,499, for reasons of record as applied to claims 1-6, 10, 11 and 21 in the Office Action mailed October 10, 2007.

On pages 9-10 of Remarks filed April 10, 2008, Applicants traverse the rejection on the grounds that Anderson et al. "do not teach the uniform differentiation of neural

crest cells into smooth muscle cells" and, thus, do not teach culturing neural crest cells under sufficient conditions, as required by Applicant's claims. Applicant asserts that their method obtains a population of cell that are "nearly 100%" smooth muscle cells. While this has been fully considered it is not found persuasive for the following reasons.

The Anderson et al. reference teaches methods for differentiating an immortalized neural crest cell line into smooth muscle cells and methods for assaying the effects of various agents on cell differentiation. The prior art teaches cells are grown in a chemically defined medium identified as L-15 medium (column 14, line 47), supplemented with chick embryo extract (column 13, lines 47-50) and specifically teaches "that smooth muscle cell differentiation is promoted by fetal bovine serum" (FIGS. 19 A, B and C) and teaches "virtually all cells obtained in SM+fetal bovine serum express high levels of SMA (FIGS. 20A, 20B)" (column 32, lines 43-45).

In light of the sections 4-13 of the instant Office Action, Examiner maintains that the Anderson et al. reference fully anticipates a method comprising culturing neural crest cells under conditions sufficient for uniform differentiation into smooth muscle cells. The method of instant claim 1 fails to distinguish over the method of the Anderson prior art, furthermore, the Anderson et al. method results in "virtually all cells" being positive for smooth muscle markers, which anticipates the instant claim requirement of "uniform" differentiation and "nearly 100%". Thus, Examiner maintains that the invention of instant claims 1-6, 10, 11, 21 and 31 is fully anticipated by the prior art.

Claim Rejections - 35 USC § 103

19. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. as applied to claims 1-6, 10, 11, 21 and 31 above.

20. The Anderson et al. reference teaches methods for differentiating an immortalized neural crest cell line into smooth muscle cells and specifically teaches "that smooth muscle cell differentiation is promoted by fetal bovine serum" (FIGS. 19 A, B and C) resulting in "virtually all cells obtained in SM+fetal bovine serum express high levels of SMA (FIGS. 20A, 20B)" (column 32, lines 43-45).

21. While the Anderson reference teaches clearly teaches that fetal bovine serum in general promotes the differentiation of neural crest cells into smooth muscle cells, the only reference to an explicit percent concentration of fetal bovine serum is one in which 5% fetal bovine serum was used (column 6, line 24). Therefore, the Anderson reference does not teach a method comprising 10% fetal bovine serum, as required by instant claim 32.

22. Section MPEP 2144.05, however, states, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Since the method of Anderson et al. comprising culturing cells in 5% leads to the result of "virtually all cells" expressing smooth muscle markers it would be obvious to one of ordinary skill in the art

that the use of 10% fetal bovine serum would yield the same results and does not constitute separate patentability of subject matter but rather an optimization of a previously patented method. Therefore, the invention as a whole is *prima facie* obvious, if not actually anticipated by the reference.

Conclusion

23. No Claim is allowed.

24. This application contains claims drawn to an invention nonelected with traverse in Paper filed on August 24, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M,W and ALT F 7 am to 3:30, T & R 5:30 -5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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